IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/555,011
Applicant	:	Nava ZISAPEL
Filed	:	October 31, 2005
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Examiner	:	Jennifer M. Kim
Docket No.	:	2007-122
Customer No.	:	06449
Confirmation No.	:	9212

Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

Declaration Pursuant to 37 C.F.R. § 1.132

I, Moshe Laudon, declare that:

1. I am the same Moshe Laudon named as an inventor on the above-referenced patent application.

2. I received my Ph.D. in neurobiochemistry from Tel-Aviv University in 1987. I was a postdoctoral fellow at Indiana University School of Medicine, in the Department of Physiology and Biophysics from 1987-1990 and followed that with a further postdoctural fellowship at the Hebrew University in Jerusalem from 1990 - 1992. Since 1992 I have been the Director of Research and Development at Neurim Pharmaceuticals Ltd. in Tel-Aviv, Israel. A copy of my C.V. is attached.

3. I have read and am familiar with the Office Action issued on June 12, 2009, by the U.S. Patent and Trademark Office in connection with this application. In that Action, the examiner rejected claims 22-42 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent 6,486,172, issued

to Myers et al., and U.S. Patent 6,353,015, issued to Oxenkrug et al. The examiner asserted that the Myers et al. reference teaches that nicotine increases cognition and attention and that the Oxenkrug et al. reference teaches that melatonin improves cognition and protects against neurotoxicity. The examiner further asserted that to use combinations of nicotine and melatonin, as set forth in the claims of the present patent application, to treat memory and cognition impairment would have been obvious because each component is well known individually for treating those conditions, and it would be expected that the combination of nicotine and melatonin would treat these conditions as well.

4. The Myers et al. patent on which the examiner relies, in part, in rejecting the claims of the present application, is directed to a new group of compounds useful as pharmaceuticals to treat cognitive and attention deficit symptoms of Alzheimer's Disease or senile dementia. The patentees note in column 17 that it is known that nicotinic cholinergic pathways control certain aspects of cognitive function and that it further is known that nicotine increases cognition and attention in humans (column 17, second full paragraph).

5. The second patent on which the examiner has relied, the Oxenkrug et al. patent, describes in an example that melatonin, N-acetyl serotonin (NAS) and their derivatives, identified as CA-15 and CA-18, were examined for cognition-enhancing and neuroprotective properties in animal and cell models of Alzheimer's Disease-type neurodegeneration. As a result of the experiments carried out, the patentees state that the chronic administration of

each of the four compounds "improves cognitive performance of AF64A-treated rats in active avoidance and in water-maze tests" and that "these compounds exerted a neuroprotective effect against the β-amyloid ...-induced neurotoxicity effect in the cerebellar granule cell culture" (column 15, line 65 - column 16, line 4).

6. The disclosures in these references do not suggest that melatonin can be administered to a subject who is receiving nicotine or a nicotine receptor agonist as nicotine replacement therapy to treat impairment of sleep quality, impairment of cognition or impairment of memory in a subject which is an adverse effect of tobacco withdrawal. It is well-known that people going through tobacco withdrawal (nicotine withdrawal) typically suffer from sleep disturbances (such as increased sleep latency, sleep fragmentation and decreased slow wave sleep with reduced sleep efficiency and increased daytime sleepiness) and, as a result, also suffer from memory or cognition impairment after awakening. Nicotine replacement therapy can help ease these adverse effects but does not fully compensate for them (see, for example, Staner L. et al., *Sleep Med.* 7(2):147-54 (2004), "Sleep effects of a 24-h versus a 16-h nicotine patch: a polysomnographic study during smoking cessation").

7. Although the examiner asserted in the outstanding Office Action that melatonin is known to improve cognition and to protect against neurotoxicity, this is a significant oversimplification of the effects of melatonin administration to humans. The effects of melatonin administration can vary significantly depending on a variety of factors, including the time of day at which it

is administered, the amount administered, and the identity of any other pharmacological agents the patient is taking. A review of the literature on melatonin administration shows that the effects of melatonin on cognition, memory and/or sleep are unpredictable--although sometimes it appears to be useful, as in the reference cited by the examiner, in other instances it either has no effect or it impairs cognition, memory and/or sleep, as discussed below.

8. For example, melatonin administration can shorten sleep latency (i.e., the time it takes to fall asleep). This is evidence of hypnotic activity, and melatonin, like hypnotic drugs, can produce a significant decrease in vigilance and performance during the first hours post-administration, particularly when administered during the day, when endogenous levels of melatonin are low. This effect is discussed in the background section of our application at page 4.

9. Similarly, it has been reported that depressed patients who received melatonin also suffer from a loss of vigilance. See Sherer, M.A. et al., *Neuroscience Letters* 58:277-282 (1985)). As also is discussed in the background section of our patent application, although melatonin administration has been shown to improve sleep latency in persons with age-related insomnia whose endogenous production of melatonin is low, there also are data which suggest that melatonin may not have sleep-inducing effects in people who produce sufficient amounts of the hormone.

10. Other references illustrate that melatonin administration often results in a decrease in cognition. A 1996 paper by H.A. Slotten and S. Krekling, *Psychoneuroendocrinology* 21(8):673-680, focuses on the

issue of whether melatonin has an effect on cognitive performance. They note that there is significant dispute in the literature as to whether melatonin has any effect on cognitive performance and that the results from a "substantial body" of previous research are equivocal. In the study reported by these researchers, cognitive performance was measured during the peak serum concentration and also at the temperature trough following melatonin administration. Four tests were administered to measure different aspects of cognitive performance. The researchers found that there was a "substantial increase" in reaction time on all four tests following melatonin administration when core body temperature was contemporaneously reduced but that no effects were observed during the serum melatonin peak. The researchers found that these results were consistent with the theory that melatonin exerts an influence on cognitive performance primarily through its hypothermic properties.

11. In addition, a study by Rogers et al. was conducted to compare neurobehavioral performance following the administration of melatonin or temazepam, a benzodiazepine hypnotic known to produce a significant reduction in neurobehavioral performance. Although the changes in performance were greater for temazepam than for melatonin, melatonin administration negatively affected performance in three of the four types of tests administered: tracking, memory and vigilance. It did not affect the results in the logical reasoning test used. The authors of the study reported that the administration of both drugs increased daytime sleepiness. See Rogers et al., *J. Sleep Res.* 12:207-212(2003).

12. In a paper published in 1997, Comperatore et al. noted that:

> Evidence of degradation of cognitive performance as a function of melatonin concentration has been reported frequently in studies designed to reveal melatonin induced side effects. An inverse relationship between dose and cognitive ability has emerged from studies in which exogenous melatonin is administered and cognitive performance is assessed for several hours thereafter. Supraphysiological levels of melatonin generally are associated with performance degradation.

(Comperatore, C.A. et al., "Aviator's Grounding Time after Melatonin Administration During Rapid Deployment Missions," NATO - RTA - AMP Meeting, 29 Sept. - 3 Oct., 1997, Rotterdam.).

The authors reported on the results of their own studies in which they administered 10 mg of melatonin either (a) right before the nightly sleep period and then evaluated the subjects' performance of cognitive tasks several hours after awakening, or (b) at 1:00 in the afternoon, after which the sbjects slept from 4:30 p.m. until 12:30 a.m., were exposed to bright light from 1:30 a.m. until sunrise and then to daylight and then were tested between 1:30 and 3:30 p.m. This second schedule mimicked a light-dark cycle 6 time zones east of the test location. In the first study, it was found that the persons treated with melatonin exhibited significantly greater vigilance errors than the placebo group, especially in the afternoon. In the second study, the persons treated

with melatonin also exhibited significantly greater vigilance errors than the placebo group, particularly shortly after awakening and in the early - mid-afternoon. The authors noted that there was a clear pattern of performance degradation in the hours immediately after administration and again after awakening but not later in the morning. The authors concluded that the results from the first study were in agreement with the concept that supraphysiological levels of melatonin are associated with cognitive performance degradation. With regard to their second study, they noted that the early-afternoon melatonin administration resulted in clear performance degradation in the hours immediately after administration but not after normal sleep. The message from this study is that although there can be some variation in the specific details, the administration of melatonin impairs cognitive performance.

13. The results of a study on daytime sleep and performance were published by Westensen et al. in 2005 in the journal *Sleep*. The authors' objective was to see if the pharmacologic enhancement of daytime sleep might help sustain optimal cognitive performance. They noted that at effective doses the hypnotic zolpidem induces sleep but also impairs performance. The authors investigated whether combining melatonin with zolpidem would promote daytime sleep without exacerbating the performance impairments seen with zolpidem alone. The test subjects had 8 hours of undisturbed nighttime sleep, then received oral zolpidem at 10:00 a.m. and/or melatonin at 10:30 a.m. The authors found that the administration of 5 mg of melatonin alone (no concomitant zolpidem administration) enhanced daytime sleep with no memory or performance impairment and that the

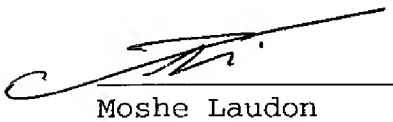
administration of zolpidem alone also enhanced daytime sleep but impaired memory and cognition. As reported in this study, therefore, the administration of melatonin had no effect on cognition and memory.

14. In a further study, Riemersma-van der lek et al. administered melatonin to elderly subjects, seeking to synchronize their circadian timing system through either light therapy or melatonin administration in an effort to ameliorate the progression of cognitive and non-cognitive symptoms often experienced by elderly patients with dementia. The authors found that the administration of melatonin shortened sleep latency but adversely affected the patients' scores on the Philadelphia Geriatric Centre Affect Rating Scale. This scale now is known as the Observed Emotion Rating Scale, and it measures pleasure, anger, anxiety/fear, sadness and general alertness. Riemersma-van der lek, R.F. et al., *JAMA* 299(22):2642-55 (2008), "Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities: a Randomized Controlled Trial."

15. As the foregoing discussion shows, it is highly inaccurate to assert, on the basis of the statements in the Oxenkrug et al. patent, that melatonin "improves cognition." All that can be learned from the Oxenkrug et al. patent is that administration of melatonin showed cognition-enhancing and neuroprotective properties in animal and cell models of Alzheimer's Disease-type neurodegeneration. This limited testing does not provide a basis for a reasonable belief that the administration of melatonin will improve sleep quality, cognition or memory in persons undergoing nicotine replacement therapy,

especially in view of the numerous examples in the literature that melatonin administration can decrease cognition and memory.

16. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Moshe Laudon

7th SEPTEMBER, 2009

Date

Curriculum vitae

First Name: **Moshe**

Name: **Laudon**

Date of Birth: **21 March 1956**

Place of Birth: **Tel-Aviv**

Nationality: **Israel**

Marital Status: **Married+2**

Work Address: **Neurim Pharmaceuticals Ltd.**
8 Hanechoshet St.
Tel-Aviv 69710
Israel

Private Address: **30 Herzel St. Kfar-Sava**
44444, Israel

Tel: **972-3-6499340**
Fax: **972-3-6494568**

972-9-7675525

Email: **Moshel@neurim.com**

EDUCATION/PROFESSIONAL

2/1992 to present	**Neurim Pharmaceuticals Ltd.**	**Director Research and Development**
08/1990 to 2/1992	The Hebrew University of Jerusalem (Israel)	**Postdoctoral Fellow**
02/1987 to 08/1990	Indiana university, School of Medicine Department of Physiology and Biophysics Indianapolis (USA)	**Postdoctoral Fellow**
10/1983 to 02/1987	Tel-Aviv University (Israel) Department of Neurobiochemistry Doctoral thesis: *Characterization and identification of the melatonin receptor*	**Ph.D.**
10/1981 to 10/1983	Tel-Aviv University (Israel) Department of Biochemistry	**M.Sc.**
10/1978 to 08/1981	Tel-Aviv University (Israel) Faculty of Life Sciences	**B.Sc.**
02/1975 to 02/1978	Israeli Defense Forces	**Tank commander**

PUBLICATIONS 1982-2002

Original papers

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3. Zisapel N, Laudon M. Dopamine release induced by electrical field stimulation of rat hypothalamus in vitro: inhibition by melatonin. Biochem Biophys Res Commun 1982;104:1610-6.
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